



**The Hospital for Sick Children  
Technology Assessment at SickKids (TASK)**

**THE USE OF BIOLOGIC RESPONSE MODIFIERS IN  
POLYARTICULAR-COURSE JUVENILE IDIOPATHIC  
ARTHRITIS**

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**REPORT HIGHLIGHTS**

*The Report Highlights consists of a summary of the full report with the same name and should be evaluated in conjunction with the full report and its appendices. Full documents are available for download at the website:*

**<http://lab.research.sickkids.ca/task/reports-theses/>**

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### **Conflicts of interest**

The authors declare that they do not have any conflicts of interest.

## Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common chronic rheumatic diseases in children, with prevalence estimates ranging from 7-400/100,000 children.

A new class of drugs, termed biologics, is increasingly used to treat JIA in pediatric patients who do not respond to conventional treatment. This report evaluates the clinical efficacy and safety evidence available for biologic drugs used in the treatment of the polyarticular subtype of JIA, and compares costs and cost-effectiveness of treatment with each biologic drug to conventional treatment.

### **Juvenile Idiopathic Arthritis**

Juvenile idiopathic arthritis is a group of heterogeneous forms of arthritis characterized by persistent joint inflammation that develops in patients younger than 16 years, lasts longer than six weeks and has no known cause. This report focuses on the more severe polyarticular-course JIA subtype, where five or more joints are affected within the first six months of illness. Patients with more severe disease experience chronic pain and stiffness, irreversible joint damage, growth abnormalities, and functional disability; these effects are expected to have a negative impact on quality of life.

### **Key Messages**

- Randomized controlled trials evaluating the use of biologic drugs in the treatment of JIA show short-term improvements in treatment response, measured by the ACR Ped 30 (American College of Rheumatologists disease improvement score).
- Longer-term treatment effects and safety, along with effects on quality of life, remain unknown. A few long-term studies have shown that the treatment effect can be maintained, although drug discontinuation due to adverse events and loss of effect also occurs.
- Costs of biologic drugs are high: annual costs range from \$14,000 to \$19,000 per child.
- Economic evaluations comparing the costs and effects of the biologic drugs etanercept, infliximab, adalimumab, and abatacept to treatment with methotrexate alone found that the incremental cost per additional ACR Ped 30 responder ranged from \$16,000 to -\$47,000.
- The long-term safety and efficacy of biologic drugs needs to be determined. These drugs may improve outcomes for JIA patients but at a high cost.

## JIA treatment strategies

**Conventional treatment** options for JIA patients include:

- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - o E.g. naproxen, ibuprofen, and indomethacin
- Glucocorticoids
  - o [E.g. prednisone](#), administered by intra-articular injection or used systemically
- Non-biologic disease-modifying anti-rheumatic drugs (DMARDs)
  - o E.g. methotrexate (MTX), sulphasalazine, cyclosporine, azathioprine, cyclophosphamide, gold, hydroxychloroquine, penicillamine, chlorambucil, leflunomide
- Physical and occupational therapy

Up to one third of patients may not have a positive treatment response to conventional treatments.<sup>1</sup>

**Biologic drugs** (i.e. manufactured from a living organism or its products, e.g. [monoclonal antibodies](#)) have been developed following a greater understanding of the inflammation pathway and its role in the pathogenesis of JIA. They can be grouped based on their mechanism of action.

- Tumour Necrosis Factor ([TNF](#))  $\alpha$  blockers:
  - o Etanercept
  - o Infliximab
  - o Adalimumab
- Interleukin blockers:
  - o Interleukin-1 blockers: Anakinra, Rilonacept
  - o Interleukin-6 blocker: Tocilizumab
- T-Cell inhibitor: Abatacept
- Anti-CD20: Rituximab

### **Adverse treatment effects with biologic drugs**

- Injection site reactions
- Increased risk of infections
- As yet unproven link between [anti-TNF- \$\alpha\$  blockers](#) and the development of lymphoma

- Long-term effects largely unknown

## Rationale

There are uncertainties regarding the long-term clinical benefits and safety following the use of biologics in JIA. Biologics have a high treatment cost, which, allied with the potential number of patients that may be eligible for treatment, may have a considerable budget impact for payers. These costs must be weighed against the potential for JIA patients to have an improved treatment response which may have long-term implications for productivity and quality of life. Long-term improvements are particularly desirable in children.

## Objectives

### *Primary objective*

To evaluate the long-term clinical efficacy and safety evidence available for biologic drugs used in the treatment of the polyarticular subtype of JIA.

### *Secondary objectives*

To compare costs and cost-effectiveness of treatment with each biologic drug to conventional treatment comprised of an optimized non-biologic DMARD regimen.

## Study population

The study population was pediatric patients with polyarticular-course JIA who presented with a suboptimal response to conventional treatment.

## Methods

### **Systematic literature review**

The peer-reviewed literature (Pubmed, Embase, Cochrane databases) and grey literature were searched for studies of biologic drugs used in the treatment of polyarticular JIA.

### **Interventions**

The report on efficacy included biologic agents for which there was evidence from randomized controlled trials (RCTs). This included etanercept, infliximab, adalimumab, abatacept and anakinra. These biologic drugs were compared to non-biologic DMARDs. The safety report included these drugs plus tocilizumab.

### **Study outcomes**

The main outcome evaluated in most of the identified studies was disease improvement defined according to the American College of Rheumatology (ACR) core set response variables<sup>2</sup>. Improvement was defined according to the ACR criteria for pediatrics, the ACR Ped 30, which is defined as an improvement  $\geq 30\%$  in at least three of the core variables<sup>1</sup> and the absence of  $\geq 30\%$  worsening in more than one variable. Other outcomes included were ACR Ped 70, disease flare rates, drug discontinuation, antibody development, and adverse events.

### **Cost analysis**

The annual cost of treatment with each biologic drug was calculated (2008 C\$). The primary cost analysis was performed from the healthcare system perspective and included healthcare resources consumed in drug administration and routine patient monitoring. A secondary cost analysis from the societal perspective included healthcare and non-healthcare costs consisting of parent/caregiver productivity losses. In the base case analysis a 40 kg patient was assumed. Univariate sensitivity analyses were conducted varying weight/body surface area and medication dose.

### **Economic evaluation**

The cost-effectiveness of biologics compared to non-biologic DMARDs, mainly MTX, in patients with polyarticular-course JIA was evaluated. Each biologic (etanercept, infliximab,

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<sup>1</sup> Global assessment of the severity of disease by the physician, global assessment of overall well-being by the patient or parent, number of active joints (joints with swelling or joints with limitation of motion and with pain, tenderness or both), number of joints with limitation of motion, erythrocyte sedimentation rate / C-reactive protein (measure of inflammation), Functional assessment (Child Health Assessment Questionnaire, CHAQ)

adalimumab, and abatacept) was modeled in a separate decision analysis and the model allowed for switches to other biologics or DMARDs in non-responders at six months. The time horizon was one year.

The effectiveness measure used was the proportion of patients who responded according to the ACR Ped 30 criteria. This measure was derived from the systematic review as the most commonly used effectiveness measure in the field. Response rates at six and 12 months were extrapolated from the various phases of the RCTs for each drug. Based on published trials and a meta-analysis, it was assumed that for the comparator intervention, optimized doses of non-biologic DMARDs, approximately 30% of patients would have a treatment response at six months. Due to the absence of data beyond this point, it was assumed that the rate of responders would remain stable for the remainder of the year.

Costs were derived from the cost analysis and included costs associated with serious adverse events. The incremental cost-effectiveness ratios (ICERs) and their 95% confidence intervals (CIs) were calculated through probabilistic sensitivity analysis (PSA). Further PSAs were carried out by varying approaches used to estimate drug effectiveness, and by varying treatment costs using a patient weight range from 10 to 70 kg.

## Clinical results

### **Systematic literature review**

Five RCTs were identified in patients with polyarticular JIA, one for each of the following biologic drugs: etanercept<sup>3</sup>, infliximab<sup>4</sup>, adalimumab<sup>5</sup>, abatacept<sup>6</sup>, and anakinra<sup>7</sup>. Several non-controlled observational studies with etanercept and infliximab were also identified (see full report).

With the exception of the infliximab study, the RCTs had a withdrawal study design and were divided into three phases. In an open-label lead-in phase (phase 1), the active biologic drug ± MTX is administered to all eligible patients. Phase 1 respondents (ACR Ped 30) were then randomized to receive either the active drug ± MTX or its matching placebo ± MTX for a period of 4-8 months depending on the study (phase 2). Phase 2 was followed by an open-label non-comparative extension phase (phase 3) where the active drug was administered to patients who were enrolled in the double-blind phase.

In the infliximab RCT, patients were randomized to receive either infliximab 3 mg/kg + MTX or matching placebo + MTX for 14 weeks. After this period, patients received infliximab 3 or 6 mg/kg + MTX until week 52. Patients could continue into an open-label extension phase.

### **Study results**

#### *Efficacy*

Results of the randomized controlled trials for etanercept, adalimumab, abatacept, and anakinra are shown in Table 1. The infliximab results are reported separately below due to differences in study design.

**Table 1: Summary of randomized controlled trial results**

<b>Biologic drug</b>	<b>Etanercept</b>	<b>Adalimumab</b>	<b>Abatacept</b>	<b>Anakinra</b>
Percentage of ACR Ped 30 responders in lead-in phase	74%	84%	65%	58%
Percentage of ACR Ped 70 responders in lead-in phase	36%	59%	28%	Not reported
Rate of drug discontinuation in lead-in phase	26%	22%	36%	42%
Rate of drug discontinuation in double-blind phase	24%	6%	18%	24%
Percentage of patients without a disease flare at end of double-blind phase, biologic ± MTX compared to ± MTX alone	72% vs. 19%	57% vs. 29% (drug alone) 63% vs. 35% (drug + MTX)	80% vs. 47%	84% vs. 60% (NS)

NS=Not statistically significant at the 5% level.

In the infliximab study, the difference in the percentage of ACR Ped 30 responders between infliximab 3 mg/kg + MTX and placebo + MTX was not statistically significant at 14 weeks (64% and 49% respectively). After 14 weeks, all patients received infliximab 3 mg/kg + MTX or 6 mg/kg + MTX. After 52 weeks approximately 75% of the patients were ACR Ped 30 responders. Between weeks six and 52, 13 (11%) patients withdrew from the study. Most discontinuations were due to lack of efficacy or adverse events.

Long-term follow-up results from the open-label extension of RCTs are available for etanercept (eight years), adalimumab (two years), and infliximab (three years). At two years, 69% of the etanercept ± MTX patients met the ACR Ped 30 criteria (intention-to-treat analysis). Analyses based on available patients showed response rates of 90% (32 patients) and 100% (11 patients) at four and eight years, respectively. In the adalimumab study



extension phase, at 104 weeks approximately 90% of 128 patients had an ACR Ped 30 response. For infliximab, 78 (64%) of the 122 patients who were initially included in the RCT went on to enter the open-label extension phase.<sup>8</sup> In 36 patients who completed 204 weeks of follow-up in the extension phase, ACR Ped 30, 50, 70, or 90 was achieved by 33 (91.7%) patients. Over the long term, drug discontinuation occurred in 10-66% (1-8 years) with etanercept, and 43-71% (1-5 years) with infliximab.

### *Safety*

The evaluation of safety included the agents studied in the RCTs listed above plus tocilizumab. During the 2-4-month open-label phase of the biologics RCTs, serious adverse events occurred in 3-7% of the patients treated with etanercept, adalimumab, abatacept, and tocilizumab. Most of the events consisted of serious infections, urticaria/anaphylactoid reaction, and one case of depression and personality disorder. During the double-blind phase, no serious adverse event was reported with the active drugs etanercept, adalimumab, abatacept, or tocilizumab. Serious infections were reported in the placebo group of the abatacept (n=2) and adalimumab (n=1) RCTs.

In the double-blind phase of the infliximab study, six (6/122, 5%) serious infections and six (6/122, 5%) serious infusion reactions were reported in infliximab-treated patients over a 9-12 month follow-up period. In the placebo arm two (3%) serious infections were reported over the initial 3.5-month phase. There were two deaths in the infliximab study. One was due to cardiac arrest following hospitalization for a severe disease flare which occurred six months after the patient discontinued infliximab 3mg/kg in the open-label extension phase. The second was in the placebo arm; the patient was hospitalized due to septic shock with cardiac function deterioration leading to death.

## **Economic analysis**

### **Cost analysis**

Table 2 shows annual healthcare system costs per patient including drug acquisition and administration, monitoring, healthcare professionals' fees, and concomitant medications.

**Table 2: Annual healthcare costs per patient for select biologics and methotrexate**

Drug	Etanercept	Infliximab	Adalimumab	Abatacept	Anakinra	Methotrexate
Annual Cost (2008C\$)	\$18,966	\$17,259	\$18,654	\$14,733	\$20,084	\$952

**Cost-effectiveness analysis**

The incremental costs per additional ACR 30 responder estimated in the cost-effectiveness analysis are shown in Table 3. Anakinra was not included as this drug is mainly used to treat systemic JIA at our institution.

**Table 3: Results of incremental cost-effectiveness analysis**

Drug	Etanercept	Infliximab	Adalimumab	Abatacept
Incremental cost per additional ACR 30 responder (95% CI)	\$26,061 (17,070, 41,834)	\$31,209 (16,659, 66,220)	\$46,711 (30,042, 75,787)	\$16,204 (11,393, 22,608)

*Sensitivity analyses*

In best case, worst case comparisons, the upper ranges of effectiveness were compared to the lower range for the comparator and vice versa. In the biologics high, DMARDs low effectiveness scenario, the ICER decreases by 33-37%, depending on the drug. In the biologics low, DMARDs high effectiveness scenarios, 7% to 58% of the simulations show the biologics having lower efficacy and higher costs than the comparator.

**Budget impact**

Assuming a prevalence of 100 JIA cases per 100,000 children yields an estimate of approximately 3,000 JIA cases in Ontario, 60% of whom may present with the polyarticular subtype (1,800). If 10% of these children are treated with biologics (n=180), and assuming drug costs of C\$15,000 per year, the annual cost to provincial payers would be C\$2.7 million. The 10% estimate is a lower limit of patients with no response to conventional treatment. Assuming that 20% of polyarticular-course JIA patients receive biologics increases the estimated cross-payer budget impact in Ontario to C\$5.4 million per year.

**Conclusions**

Current evidence shows a short-term improvement in disease status following treatment with biologics in patients with polyarticular JIA who had previously had an inadequate response to conventional treatment. It is believed that better control of the disease may result in improvement in important long-term clinical outcomes, such as functional disability, which may affect social functioning, employment, and quality of life. Long-term treatment outcomes data, however, are not presently available.

Annual treatment costs with biologics are in the range of C\$14,000 to C\$19,000 depending on the drug and dose used (40 kg patient). The use of biologics has the potential for considerable annual budget impacts to payers, possibly as high as C\$5 million in Ontario.

The economic models were based on the best evidence currently available. The analyses were limited to a short-term time horizon of one year, as the uncertainty in estimates beyond this time was too great to allow for meaningful extrapolation. Utility estimates for health states were not available, so ICERs represent the incremental cost per additional treatment responder. The choice of outcome measure (ACR Ped 30) was based on RCTs and may not be as clinically relevant as more restrictive definitions of response. This makes it challenging to interpret and compare these results to other studies and set thresholds for clinical and resource allocation decisions.

Along with a potential for improvement in clinical outcomes in some patients comes a potential for a considerable budget impact to payers given the number of patients that may need treatment and the length of treatment. Moreover, important questions of long-term safety persist. All these factors need to be considered and require further evaluation.

## **REFERENCES**

1. Ruperto N, Murray KJ, Gerloni V, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum 2004;50(7):2191-201.
2. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis & Rheumatism 1997;40(7):1202-9.
3. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342(11):763-9.
4. Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007;56(9):3096-106.
5. Lovell DJ, Ruperto N, Goodman S, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 2008;359(8):810-20.
6. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008;372(9636):383-91.

7. Ilowitz N, Porras O, Reiff A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol 2008.
8. Lovell DJ, Ruperto N, Cuttica R, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Presented at the ACR/ARHP Annual Scientific Meeting 2008.